

## REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Previous claims 41-44 are replaced by new claims 45-48. New claims 45 and 47 correspond to previous claim 41. New claim 46 corresponds to previous claim 43. New claim 48 corresponds to previous claim 44.

Applicants do not believe the new claims introduce any new matter. The concept that the vertebrate is a rodent is supported by the specification at page 7, lines 4-5. The concept that the expression vector comprises a shRNA construct under the control of an ubiquitous promoter and sequences suitable for targeted integration into the polymerase II dependent locus is supported by the specification in the fourth paragraph on page 7. Finally, the concept that the integration is at a specific site is supported through out the specification, for example, the same fourth paragraph on page 7.

Turning to the open issues, claim 41 was rejected under 35 USC § 101 as claiming non-statutory subject matter, namely humans. In response, Applicants point out that claim 41 is replaced by new claims 45 and 47, which are limited, respectively, to “[a] rodent” and to “[a] tissue or cell culture obtained from a rodent.” Consequently, the present claims do not read on humans.

Claims 41-43 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, new claim 47 recites “obtained from a rodent” as suggested by the Examiner.

Moreover, none of the new claims recites “preferably.” Finally, claim 46, which replaces claim 43, is properly dependent on claim 45.

Claims 41-43 were rejected under 35 USC § 112, first paragraph, as being broader than the enabling disclosure. In response, Applicants note that the Examiner concedes enablement for mice. Applicants respectfully submit that persons skilled in the art would reasonably expect the invention to be applicable to rodents and to be operable therein. Accordingly, Applicants further submit that the present claims limited to rodents and tissue and cell cultures obtained therefrom are enabled by the instant specification.

Claim 44 was rejected under 35 USC § 102(b) as being anticipated by Paddison, Genes & Dev., 16: 948-958 (2002). In response, Applicants respectfully submit that Paddison does not teach an expression vector having the combination of sequences required by new claim 48, which replaces rejected claim 44. Consequently, Applicants respectfully submit that this rejection is overcome.

Claims 41-43 were rejected under 35 USC § 102(b) as being anticipated by McCaffrey et al. (“McCaffrey”), Nature, 418: 38-39 (2002). In response, Applicants point out that the Examiner indicates at the top of page 9 of the Office Action that this rejection can be overcome by stating the expression vector is stably integrated into the genome of the mouse. As noted above, the present claims are directed to a rodent or a tissue or cell culture obtained therefrom. Nevertheless, new main claims 45 and 47 require such stable integration and, moreover, at a polymerase II dependent locus, which the Examiner concedes McCaffrey also does not teach. Consequently, Applicants respectfully submit that this rejection also is overcome.

Claims 41-43 were rejected under 35 USC § 102(e) as being anticipated by Beach, US 2003/0084471. In response, Applicants point out that the Examiner concedes that Beach does not describe stable integration at a polymerase II dependent locus, which is a requirement of the present claims. Consequently, Applicants respectfully submit that Beach cannot anticipate the present claims.

Claims 41-44 were rejected under 35 USC § 103(a) as being obvious over Beach, Bronson et al. (“Bronson”), PNAS USA, 93: 9067-9072 (1996), and Soriano et al. (“Soriano”), US 6,461,864. In response, Applicants respectfully submit that the cited combination of references does not make out a *prima facie* case of the obviousness of the instant claims.

Soriano describes a method for the production of transgenic animals that ubiquitously express a heterologous gene inserted into the Rosa26 locus through homologous recombination. In this configuration, the endogenous Rosa26 promoter drives transgene expression via a splice acceptor sequence. Importantly, Soriano does not determine the activity of exogenous promoters when stably inserted into the Rosa26 locus. Therefore, Soriano does not provide persons skilled in the art with motivation to insert transgenes under the control of an exogenous promoter into the Rosa26 locus to achieve ubiquitous expression.

In short, the combination of Beach, Bronson and Soriano does not lead to the present invention. Beach discloses the use of double-stranded RNA molecules for RNA interference. Beach suggests that shRNA can be expressed in transgene animals. However, Beach does not provide any teaching how a shRNA construct can be stably integrated into the genome of animals, let alone the integration position or the arrangement of the integration construct that must be used to effectively induce shRNA expression. Without those teachings, and in view of

Soriano's failure to provide motivation, the combination of Beach and Soriano would not have led persons skilled in the art to the present invention.

Bronson is cited only for general background teachings and does not in any way overcome the above-noted defects in the combination of Beach and Soriano. Consequently, the combination of Beach, Bronson and Soriano similarly fails to make out a *prima facie* case of the obviousness of the present claims.

Claims 41-44 were provisionally rejected on the ground of obviousness-type double patenting as being unpatentable over claims 27 and 30 of copending application Serial No. 10/685,837. In response, Applicants point out that this rejection is provisional and, as such, Applicants respectfully request that this issue be held in abeyance until allowable subject matter is indicated, at which time Applicants will take appropriate action, for example, prove patentable distinctness or file a suitable terminal disclaimer.

Finally, the application was objected to for failure to comply with the applicable Sequence Listing rules. In particular, the Examiner objects that Tables 1 and 2 lack sequence identifiers. In response, Applicants have amended the specification above to provide the sequence identifiers. Applicants do not believe the amendments introduce any new matter.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

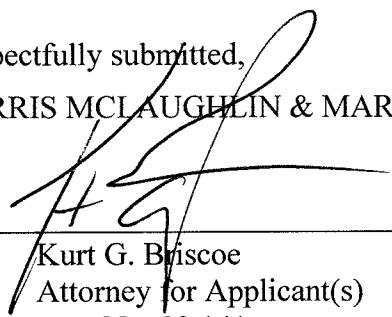
Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to

telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,  
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